

# Outcomes of Lung Transplantation for Bronchiolitis Obliterans after Hematopoietic Stem Cell Transplantation Compared with Those for Idiopathic Pulmonary Fibrosis

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**Purpose:** Bronchiolitis obliterans syndrome (BOS) can develop as a manifestation of graft-versus-host disease following allogeneic hematopoietic stem cell transplantation (allo-HSCT), and may ultimately require lung transplantation (LT). However, reports on LT outcomes for BOS after allo-HSCT are limited. This study aimed to compare the outcomes of LT for BOS following allo-HSCT with those for idiopathic pulmonary fibrosis (IPF).

**Materials and Methods:** A total of 487 patients underwent LT between January 2010 and August 2023. Among them, the baseline characteristics and outcomes of 35 patients with BOS following allo-HSCT and 216 patients with IPF were analyzed.

**Results:** The BOS group was younger and had a lower body mass index (BMI) compared to the IPF group (33.7±11.9 years vs. 59.7±7.3 years,  $p<0.001$ ; 17.6±3.7 kg/m<sup>2</sup> vs. 22.0±3.6 kg/m<sup>2</sup>,  $p<0.001$ , respectively). The proportion of male patients was lower in the BOS group than in the IPF group (54.3% vs. 84.3%,  $p<0.001$ ). Preoperative ventilator support was more common in the BOS group compared to the IPF group (62.9% vs. 32.4%,  $p=0.001$ ). In Kaplan–Meier survival analysis, the 5-year survival rate was significantly higher in the BOS group than in the IPF group (71.0% vs. 44.9%,  $p=0.022$ ). In the Cox proportional hazards model, age was the only factor significantly associated with survival [hazard ratio (95% confidence interval): 1.04 (1.02–1.07),  $p<0.001$ ].

**Conclusion:** The survival rate of the BOS group was not inferior to that of the IPF group after adjusting for sex, age, and BMI. Therefore, LT should be actively considered as a treatment option for patients with BOS following allo-HSCT.

**Key Words:** Lung transplantation, bronchiolitis obliterans syndrome, late onset non-infectious pulmonary complication, allogeneic hematopoietic stem cell transplantation, graft-versus-host disease, survival

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## INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an established treatment for various hematological malignancies. Although survival rates after allo-HSCT for hematologic diseases have improved, allo-HSCT can also lead to serious complications, such as graft-versus-host disease (GVHD).<sup>1</sup> GVHD can involve multiple organs, including the skin, gastrointestinal tract, liver, and lung, and is classified according to the severity and extent of involvement.<sup>2</sup> Pulmonary GVHD is particularly associated with morbidity and mortality in allo-HSCT

recipients; it is classified into infectious and non-infectious forms.<sup>3</sup> With improvements in infection management, the relative importance of late-onset non-infectious conditions (LON-PIC) has increased. Among these, bronchiolitis obliterans syndrome (BOS) is the most common manifestation.<sup>4</sup>

BOS affects 4%–5% of allo-HSCT recipients and up to 15% of those who develop chronic GVHD.<sup>5–7</sup> Despite recent advancements in immunosuppressive therapy, the prognosis of BOS following allo-HSCT remains poor. Lung transplantation (LT) has emerged as a potential definitive treatment for BOS following allo-HSCT, with some studies reporting encouraging outcomes. However, comprehensive analyses are limited due to the rarity of the disease and the small number of reported cases.<sup>4,8–13</sup>

This study aimed to investigate the characteristics and outcomes of patients who underwent LT for BOS following allo-HSCT. In addition, we compared these patients with those who received LT for idiopathic pulmonary fibrosis (IPF), the most common indication for LT, to characterize the clinical features and survival outcomes of the BOS group.

## MATERIALS AND METHODS

### Patients

Between January 2010 and August 2023, 487 patients underwent LT at a single institution. Based on the preoperative diagnosis, patients were categorized into two groups: 35 with BOS following allo-HSCT and 216 with IPF. This study was approved by the Institutional Review Board (IRB No. 2024-1537-001), and the requirement for informed consent was waived due to its retrospective design.

### Data acquisition

Basic demographic and clinical characteristics were retrospectively reviewed using patient medical records. The diagnosis of BOS was confirmed according to the 2014 National Institutes of Health consensus clinical criteria.<sup>2</sup> Extensive GVHD was defined as involvement of organs other than the lungs and skin. Severe adhesion was defined as a case in which either lung exhibited marked pleural adhesion. Ischemic time was defined as the interval between donor aortic cross-clamping and completion of pulmonary anastomosis. Postoperative bleeding was defined as either a total chest tube drainage volume >1000 mL within 24 hours or the need for reoperation due to bleeding. Primary graft dysfunction (PGD) grade was assessed according to the International Society for Heart and Lung Transplantation (ISHLT) guidelines, and the proportion of patients with grade 3 PGD (PGD G3) was recorded.<sup>14</sup> Pulmonary function tests (PFTs) were routinely performed at 1, 3, 6, and 12 months post-transplantation.

### Statistical analysis

Continuous variables are presented as mean±standard deviation

and were analyzed using independent-sample t-tests. Categorical variables are presented as numbers and percentages and were analyzed using the chi-square test. Survival analysis was performed using Kaplan–Meier survival curves and Cox proportional hazards regression models. A *p*-value<0.05 was considered statistically significant. All analyses were conducted using RStudio version 1.4.555 and SPSS version 27.0 (IBM Corp., Armonk, NY, USA).

## RESULTS

### Basic demographic and clinical characteristics

Pre-transplant characteristics of patients with BOS following allo-HSCT are summarized in Table 1. The mean age at the time of allo-HSCT was 27.4 years, and acute myeloid leukemia was the most common indication for transplantation (n=15, 43.3%). Extensive GVHD was observed in 65.7% of patients (n=23). The median interval from allo-HSCT to the diagnosis of BOS was 16 months, and the median interval from BOS to LT was 26 months.

**Table 1.** Pre-Transplant Characteristics of Patients with BOS Following Allo-HSCT (n=35)

	Value
Age at time of allo-HSCT (yr)	27.4±10.5
Preoperative FEV <sub>1</sub>	1.33±0.52 (L), 45.1±16.7 (%)
Preoperative FVC	1.65±0.60 (L), 42.1±13.5 (%)
Preoperative FEV <sub>1</sub> /FVC (%)	83.08±17.6
Indication for HSCT (%)	
SAA	5 (14.3)
AML	15 (43.3)
ALL	11 (31.4)
Others	CML (1), MDS (1), PTCL (1), DLBCL (1)
Type of HSCT	
R-BMT	7 (20.0)
R-PBSCT	12 (34.3)
UR-BMT	3 (8.6)
UR-PBSCT	13 (37.1)
Chronic GVHD	
Lung alone	9 (25.7)
Skin and lung involved	3 (8.5)
Extensive	23 (65.7)
Interval (HSCT to BOS), months	16 (4–180)
Interval (BOS to LT), months	26 (2–140)

BOS, bronchiolitis obliterans syndrome; allo-HSCT, allogeneic hematopoietic stem cell transplantation; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; SAA, severe aplastic anemia; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; PTCL, peripheral T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; R-BMT, related donor bone marrow transplantation; UR-PBSCT, unrelated donor peripheral blood stem cell transplantation; GVHD, graft-versus-host disease; LT, lung transplantation. Data are presented as mean±standard deviation or n (%).

LT characteristics for patients with BOS following allo-HSCT and those with IPF are presented in Table 2. Patients with BOS were significantly younger than those with IPF (33.7 years vs. 59.7 years,  $p<0.001$ ) and had a lower proportion of male patients (54.3% vs. 84.3%,  $p<0.001$ ). Compared to patients with IPF, those with BOS had a lower body mass index (BMI) (17.6 kg/m<sup>2</sup> vs. 22.0 kg/m<sup>2</sup>,  $p<0.001$ ) and were more likely to require ventilator support prior to LT (62.9% vs. 32.4%,  $p=0.001$ ). Preoperative laboratory findings revealed that BOS patients had significantly higher serum albumin levels compared to IPF patients (3.7 g/dL vs. 3.4 g/dL,  $p=0.014$ ). No significant differences were observed in other preoperative characteristics, intraoperative findings, or postoperative complications between the two groups.

### Survival analysis in the BOS following allo-HSCT group

Kaplan–Meier survival analyses were performed based on stem cell source, donor type, HSCT indication, and GVHD extent. Survival analysis according to stem cell source [bone marrow transplantation (BMT) vs. peripheral blood stem cell transplan-

tation (PBSCT)] demonstrated a significant difference (log-rank test,  $p=0.012$ ) (Fig. 1A). In contrast, donor type, interval between HSCT and LT, and GVHD extent were not significantly associated with survival (Fig. 1B–D).

### Survival analysis and Cox proportional hazard model between BOS following allo-HSCT and IPF

The Kaplan–Meier survival curve demonstrated a significant difference between the groups (log-rank test,  $p=0.022$ ) (Fig. 2). The 5-year survival rates for BOS following allo-HSCT and IPF were 71.0% and 44.9%, respectively. The survival rate of the BOS group was comparable to that of all lung transplant recipients aged <60 years in the ISHLT registry.<sup>15</sup>

A Cox proportional hazards model was constructed, adjusting for age, sex, BMI, and diagnosis group. Age was identified as a significant factor affecting survival [hazard ratio (HR) [95% confidence interval (CI)]: 1.04 (1.02–1.07),  $p<0.001$ ] (Fig. 3). The diagnosis group (BOS vs. IPF) was not significantly associated with survival [HR (95% CI): 0.69 (0.29–1.62),  $p=0.4$ ].

**Table 2.** Comparison of Lung Transplantation Characteristics between Patients with BOS Following Allo-HSCT and Those with IPF

	BOS following HSCT (n=35)	IPF (n=216)	<i>p</i>
Age (yr)	33.7±11.9	59.7±7.3	<0.001*
Sex, male	19 (54.3)	182 (84.3)	<0.001*
BMI (kg/m <sup>2</sup> )	17.6±3.7	22.0±3.6	<0.001*
Preoperative ventilator	22 (62.9)	70 (32.4)	0.001*
Preoperative ECMO	7 (20.0)	71 (32.9)	0.168
Albumin (g/dL)	3.7±0.69	3.4±0.67	0.014*
Total protein (g/dL)	6.0±0.94	6.3±1.22	0.132
Severe pleural adhesion	18 (51.4)	100 (50.0)	0.876
Ischemic time (min)	246.6±79.9	226.2±74.3	0.140
Contra-ischemic time (min)	335.3±90.2	321.4±75.7	0.334
Intraoperative blood loss (cc)	2771.4±2302	3028.0±2617	0.587
Total operation time (min)	391.8±95.9	390.1±83.6	0.916
Dialysis	5 (14.3)	38 (18.5)	0.544
Postoperative bleeding	7 (20.0)	41 (20.1)	0.989
PGD G3 T0	15 (42.9)	111 (55.5)	0.166
PGD G3 T24	11 (31.4)	74 (37.0)	0.527
PGD G3 T48	6 (17.1)	56 (28.0)	0.179
PGD G3 T72	6 (17.1)	39 (19.5)	0.744
ICU stay (day)	10.2±12.9	9.2±7.9	0.663
Donor age (yr)	43.5±12.4	43.8±12.7	0.895
Donor sex, male	26 (74.3)	148 (67.0)	0.392
Donor PaO <sub>2</sub> /FiO <sub>2</sub> ratio	464.4±98.3	452.6±92.2	0.491

BOS, bronchiolitis obliterans syndrome; allo-HSCT, allogeneic hematopoietic stem cell transplantation; IPF, idiopathic pulmonary fibrosis; BMI, body mass index; ECMO, extracorporeal membrane oxygenation; PGD G3, primary graft dysfunction grade 3; T0, immediate postoperative; T24, postoperative 24 hours; T48, postoperative 48 hours; T72, postoperative 72 hours; ICU, intensive care unit.

Data are presented as mean±standard deviation or n (%).

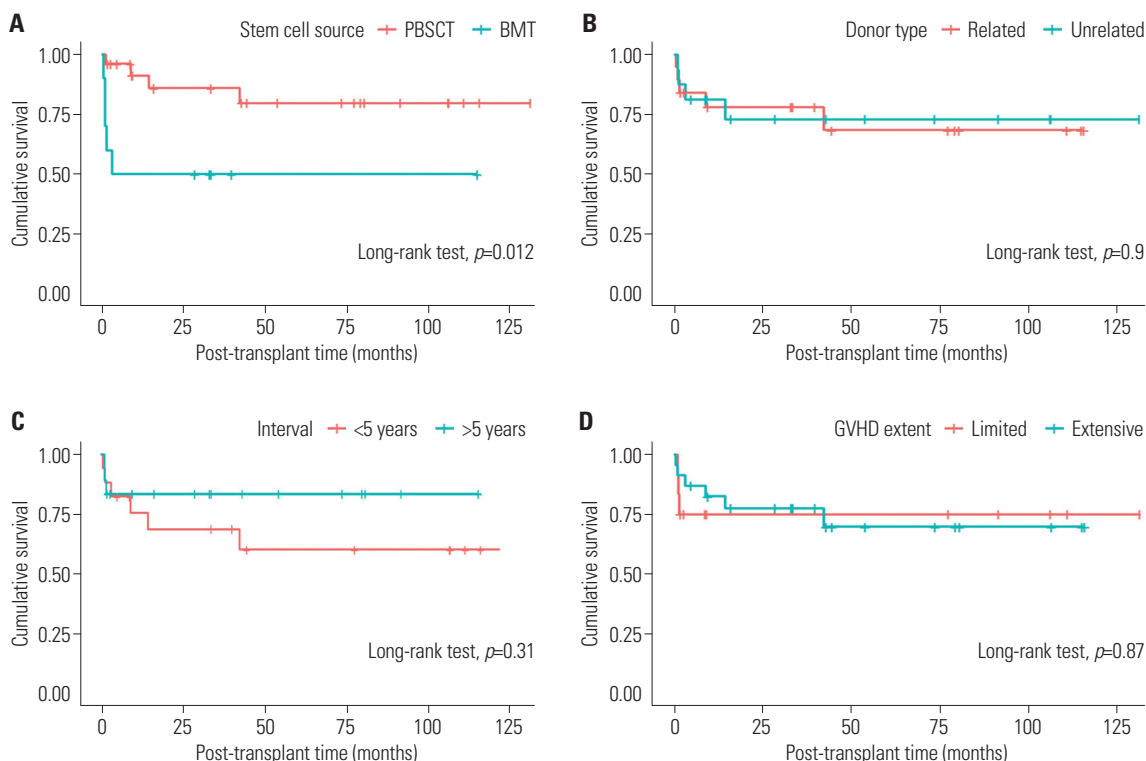
\* $p<0.05$ .

### PFTs after LT between groups

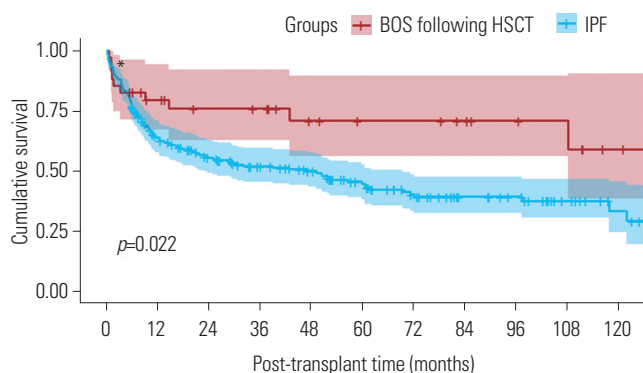
During the 12-month follow-up period, both forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV<sub>1</sub>) improved in the BOS and IPF groups (Fig. 4). Preoperatively, the FVC was 1.65 L (42.1%) in the BOS group and 1.71 L (44.3%) in the IPF group, while the FEV<sub>1</sub> was 1.33 L (45.1%) and 1.26 L (43.2%), respectively. At 1 month postoperatively, the FVC increased to 1.90 L (42.1%) in the BOS group and 2.11 L (54.0%) in the IPF group, and the FEV<sub>1</sub> increased to 1.72 L (60.4%) and 1.87 L (63.2%), respectively. At 3 months postoperatively, the FVC was 2.03 L (52.1%) in the BOS group and 2.17 L (56.4%) in the IPF group, while the FEV<sub>1</sub> was 1.75 L (59.7%) and 1.86 L (63.0%), respectively. At 6 months, the FVC was 2.25 L (58.9%) and 2.32 L (59.7%), and the FEV<sub>1</sub> was 1.86 L (64.3%) and 1.94 L (65.0%) in the BOS and IPF groups, respectively. At 12 months, the FVC was 2.59 L (64.4%) in the BOS group and 2.48 L (63.7%) in the IPF group, and the FEV<sub>1</sub> was 2.14 L (70.4%) and 2.03 L (67.5%), respectively. No significant differences in FVC or FEV<sub>1</sub> were observed between the two groups at any time point.

## DISCUSSION

In this study, we compared patients who underwent LT for BOS following allo-HSCT with those who underwent LT for IPF. Among patients with BOS, the stem cell source was significantly associated with survival outcomes, with a 5-year survival rate of 84.0% for PBSCT recipients and 50.0% for BMT recipients ( $p=0.012$ ). When comparing the BOS and IPF groups, significant differences were observed in sex distribution, age, BMI, preoperative serum albumin levels, and the need for preoperative ventilator support. Kaplan–Meier survival analysis demonstrated superior survival in the BOS group compared to the



**Fig. 1.** Kaplan–Meier survival curves in the BOS group. (A) Survival according to stem cell source (BMT vs. PBSCT). (B) Survival according to donor type (related vs. unrelated). (C) Survival according to the interval between HSCT and LT. (D) Survival according to GVHD extent (limited vs. extensive). PBSCT, peripheral blood stem cell transplantation; BMT, bone marrow transplantation; GVHD, graft-versus-host disease; BOS, bronchiolitis obliterans syndrome; HSCT, hematopoietic stem cell transplantation; LT, lung transplantation.



**Fig. 2.** Kaplan–Meier survival curves comparing the BOS and IPF groups. The log-rank test indicated a significant difference ( $p=0.022$ ). BOS, bronchiolitis obliterans syndrome; HSCT, hematopoietic stem cell transplantation; IPF, idiopathic pulmonary fibrosis.

IPF group (5-year survival: 71.0% vs. 44.9%,  $p=0.022$ ). However, after adjusting for age, BMI, and sex using a Cox proportional hazards model, no significant difference in survival was observed between the groups [HR (95% CI): 0.69 (0.29–1.62),  $p=0.4$ ]. Although no significant difference was found between the two groups in terms of pulmonary function, both FVC and FEV<sub>1</sub> consistently improved over the 12-month postoperative follow-up period.

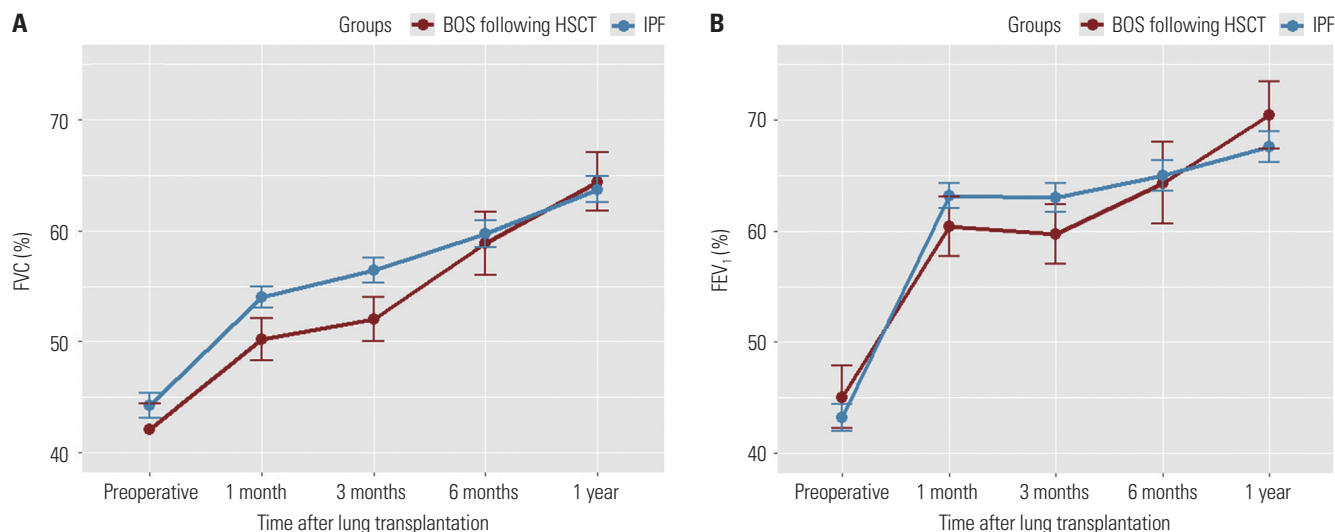
Among patients with BOS, the PBSCT group showed a high-

Variable	N	Hazard ratio	p
Diagnosis (BOS vs IPF)	251	0.69 (0.29, 1.62)	0.4
Age (years)	251	1.04 (1.02, 1.07)	<0.001
Sex (Male)	251	1.13 (0.69, 1.83)	0.6
BMI (kg/m <sup>2</sup> )	251	1.01 (0.96, 1.06)	0.8

**Fig. 3.** Cox proportional hazards analysis in the BOS and IPF groups. The model was adjusted for age, sex, BMI, and diagnosis. BOS, bronchiolitis obliterans syndrome; IPF, idiopathic pulmonary fibrosis; BMI, body mass index.

er survival rate compared to the BMT group (Fig. 1A). To explore potential reasons for this difference, a subgroup analysis was conducted comparing PBSCT and BMT recipients. Post-operative bleeding was more frequent in the BMT group ( $p=0.012$ ). A previous study reported that BMT recipients experienced delayed platelet recovery and greater transfusion requirements during the early post-transplant period, which may have contributed to the increased risk of postoperative bleeding.<sup>16</sup> To the best of our knowledge, no other studies have spe-





**Fig. 4.** Pulmonary function test results during the postoperative follow-up period in the BOS and IPF groups. (A) Relationship between the percentage of predicted FVC and time. (B) Relationship between the absolute value of FEV<sub>1</sub> and time. BOS, bronchiolitis obliterans syndrome; HSCT, hematopoietic stem cell transplantation; IPF, idiopathic pulmonary fibrosis; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 second.

cifically evaluated LT outcomes based on stem cell source. Although a meta-analysis of survival after HSCT showed no significant survival difference between PBSCT and BMT, a separate study investigating risk factors for BOS found that PBSCT recipients had a higher incidence of BOS compared to those who received related BMT.<sup>17,18</sup> Other factors, including donor type, transplantation interval, and GVHD extent, were not associated with differences in survival.

The optimal timing for LT after allo-HSCT remains controversial due to the risk of relapse of the primary hematologic malignancy. The ISHLT guidelines recommend avoiding LT within 2 years of HSCT and suggest considering it after approximately 5 years.<sup>19</sup> In a meta-analysis with a 60-month follow-up, patients with an interval >60 months between HSCT and LT showed a trend toward improved survival ( $p=0.065$ ).<sup>4</sup> In the present study, only 2 patients (5.7%) underwent LT within 24 months after HSCT; therefore, survival analysis for this subgroup was not performed. Additionally, 17 of 35 patients (48.5%) underwent LT within 60 months of HSCT; however, Kaplan-Meier analysis revealed no significant difference in survival based on this interval (log-rank test,  $p=0.31$ ) (Fig. 1C). One patient in this study exhibited clinical findings suggestive of recurrence of hematologic malignancy 10 years after LT; however, a definitive evaluation was not possible due to the patient's deteriorating condition.

To investigate the characteristics of BOS following allo-HSCT, a comparative analysis was conducted with patients diagnosed with IPF, the most common indication for LT in Korea.<sup>20</sup> Compared to the IPF group, patients in the BOS group were younger, had a lower proportion of males, a lower BMI, and a higher rate of preoperative ventilator support. Given the lower BMI and greater need for preoperative ventilator care, poorer postoperative rehabilitation and pulmonary function were anticipated; however, follow-up PFTs and other postoper-

ative outcomes did not differ significantly from those of the IPF group (Table 2 and Fig. 4).<sup>21,22</sup> This may be attributed to the younger age and higher serum albumin levels of the BOS group, which may have offset the anticipated negative factors.<sup>23</sup>

The Kaplan-Meier survival curve demonstrated a significant difference between the groups, with 5-year survival rates of 71.0% for BOS following allo-HSCT and 44.9% for IPF ( $p=0.022$ ) (Fig. 2). Although some heterogeneity was present, previous meta-analyses have reported survival rates of BOS following allo-HSCT similar to those in our study. However, these meta-analyses found no significant difference in survival between the BOS and fibrosis groups, and another study reported comparable survival outcomes between BOS following allo-HSCT and other disease entities.<sup>4,24</sup> In our analysis, despite an observed difference in unadjusted survival rates, no significant difference was found between BOS and IPF in the Cox proportional hazards model after adjusting for age, sex, and BMI [HR (95% CI): 0.69 (0.29–1.62),  $p=0.4$ ]. Given the younger average age and non-inferior survival outcomes of the BOS group compared to the IPF group, LT should be actively considered in eligible BOS patients.

In this study, a total of nine patients in the BOS group died, six of whom died within 90 days postoperatively. The 90-day postoperative mortality rate in the BOS group was 17.1%, which is higher than the generally reported rate of approximately 10%.<sup>25</sup> The remaining three patients died of infections at 9, 14, and 42 months after transplantation. When comparing the mortality and survival groups, ischemic time was significantly shorter in the survival group ( $225.8 \pm 74$  minutes vs.  $299.9 \pm 64$  minutes,  $p=0.012$ ).

This study has several limitations. BOS and IPF are inherently distinct disease entities; BOS shares more pathophysiological characteristics with obstructive lung diseases such as COPD.

However, in our country, COPD accounts for only a small proportion of indications for LT. Although cystic fibrosis (CF) patients are similar in age to those with BOS, CF is extremely rare in Korea, making direct comparison infeasible. We also considered comparing BOS following allo-HSCT with BOS occurring after LT; however, the number of such cases was small and involved retransplantation, limiting the feasibility of analysis. IPF was therefore selected as the comparator group, as it represents the most common indication for LT in Korea.

We attempted to perform propensity score matching to adjust for age and sex, but only 12 matched patients remained, making comparative analysis inappropriate. Instead, we conducted a multivariable survival analysis using a Cox proportional hazards model adjusted for age, sex, and BMI, which showed no significant difference in survival between disease groups [HR (95% CI): 0.69 (0.29–1.62),  $p=0.4$ ].

This was a retrospective observational study with a small sample size from a single center; therefore, the results should be interpreted with caution. Additionally, 2 patients (5.7%) did not meet the 24-month interval between HSCT and LT recommended by the ISHLT guidelines, precluding subgroup analysis. Future studies with a larger cohort may allow for a more detailed investigation of this issue.

In conclusion, compared with patients with IPF, those with BOS were younger, had a lower BMI, were more likely to be female, and more frequently required preoperative ventilator support. The BOS group demonstrated superior survival compared to the IPF group, with comparable outcomes observed after adjustment for age, sex, and BMI. These findings suggest that LT should be actively considered as a treatment option for patients with BOS following allo-HSCT. Although the results of this study may inform clinical decision-making for this patient population, multicenter studies with larger cohorts are warranted to validate and strengthen these findings.

## AUTHOR CONTRIBUTIONS

**Conceptualization:** Jin Gu Lee. **Data curation:** Ha Eun Kim, Young Ho Yang, A La Woo, Eun Young Kim, Moo Suk Park, and Song Yee Kim. **Formal analysis:** Bong Suk Park and Jin Gu Lee. **Investigation:** Bong Suk Park. **Methodology:** Dae Joon Kim, Chang Young Lee, Byung Jo Park, and Jin Gu Lee. **Project administration:** Jin Gu Lee. **Resources:** Ha Eun Kim, Young Ho Yang, A La Woo, Eun Young Kim, Moo Suk Park, and Song Yee Kim. **Software:** Bong Suk Park. **Supervision:** Dae Joon Kim, Chang Young Lee, Byung Jo Park, and Jin Gu Lee. **Validation:** Dae Joon Kim, Chang Young Lee, Byung Jo Park, and Jin Gu Lee. **Visualization:** Bong Suk Park. **Writing—original draft:** Bong Suk Park. **Writing—review & editing:** Ha Eun Kim, Young Ho Yang, Dae Joon Kim, Chang Young Lee, and Byung Jo Park. **Approval of final manuscript:** all authors.

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